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NEUROSCIENCE AND THE LAW — SCIENCE AND SOCIETY

Effects of Schedule I drug laws on neuroscience research and treatment innovation

David J. Nutt, Leslie A. King and David E. Nichols

Abstract | Many psychoactive drugs are used recreationally, particularly by young people. This use and its perceived dangers have led to many different classes of drugs being banned under national laws and international conventions. Indeed, the possession of cannabis, 3,4-methylenedioxy-*N*-methylamphetamine (MDMA; also known as ecstasy) and psychedelics is stringently regulated. An important and unfortunate outcome of the controls placed on these and other psychoactive drugs is that they make research into their mechanisms of action and potential therapeutic uses — for example, in depression and post-traumatic stress disorder — difficult and in many cases almost impossible.

A large number of different classes of psychoactive drugs are controlled ('banned') under national laws and international conventions. These controls are supposedly designed to reduce the use of the drugs because of the harms they cause, even though in many cases these harms may be greatly overstated (see below) and may be less than those of some prescription drugs or even legal drugs such as alcohol[1,2]. Importantly, the harms that derive from the controls themselves may exceed the harms of the drugs, especially when one considers societal harms. For example, the legal consequences of arrest for drug possession are extreme. In the United States, in 2011, 660,000 people were arrested for possession of cannabis (marijuana) and over 50,000 are in prison on cannabis possession charges[3]. In the United Kingdom, about 1 million people have been convicted for cannabis possession (numbers for people imprisoned are not available). Such penalties limit careers and can destroy livelihoods and families, raising the question of whether any harmful effect of marijuana justifies a draconian penalty such as imprisonment — sometimes for life.

A small number of psychoactive drugs, including opiates and some stimulants (amphetamines), are allowed to be used as treatments for medical conditions such as pain and attention-deficit disorders, respectively. Others, such as cannabis, 3,4-methylenedioxy-*N*-methylamphetamine (MDMA; also known as ecstasy) and psychedelics, are controlled more stringently and are therefore not available for therapeutic use. This distinction is not based on the relative harms of these drugs; it is simply a historical accident — older drugs had medical uses before the era of the international conventions and the subsequent 'War on Drugs', which allowed them to escape the most stringent controls, as described below.

In this Perspective, we discuss the current state of affairs regarding research using controlled substances and show how the legal approach to drug control has hindered research into the therapeutic potential of cannabis, stimulants and psychedelic drugs. We argue that the approach of putting penalization of illegal drug possession at the fore of regulatory approaches has severely limited — and continues to limit — neuroscience research and the discovery of new treatments for brain disorders.

The current legal situations

In most countries, the legal control of psychoactive drugs stems from three United Nations treaties: the 1961 Single Convention on Narcotic Drugs[4], the 1971 Convention on Psychotropic Substances[5] and the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances[6]. The 1971 convention makes it clear that use of Schedule I substances, such as MDMA, psilocybin and lysergic acid diethylamide (LSD; also known as lysergide), is to be severely restricted. Parties to this convention are to "prohibit all use except for scientific and very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of their Governments or specifically approved by them" (REF. 5). This means that research using these substances can be undertaken only after approval of a government agency. In the United States, this agency is the Drug Enforcement Administration (DEA), whose mission it is, in part, to prevent the diversion of controlled substances. In the United Kingdom, control is exercised by the Home Office, which can provide sites such as laboratories and hospitals with licences to produce or hold these drugs. Production or use of controlled drugs without such a licence is illegal and can bring severe penalties of up to life imprisonment.

The decisions that were made about which drugs should be controlled under this legislation seem to be unclear and inconsistent and may have been made for political rather than health-related reasons. This is because for many drugs the decisions were made before modern scientific methods allowed a proper understanding of their pharmacology and toxicology. As a result, the decision to list MDMA, psilocybin and LSD as United Nations Schedule I drugs was not based on any consideration of their physical harms but on the assumption that there were no medical benefits. Indeed, recent analyses have shown that there is no relation between the harms of a range of psychoactive drugs and their current legal status in the United Kingdom[1,2]. However, there is no process for reviewing these decisions at national or United Nations levels.

The United Nations signatory countries apply their own internal drug control laws and regulations. These laws and regulations differ somewhat between the United States and the United Kingdom (other European countries each have different regulations, which are not discussed here), as does the numbering of the different drug classes. In the United Nations conventions and the US Controlled Substances Act, roman numerals are used for the Schedules (I, II, and so on), whereas the UK Misuse of Drugs Regulations use Arabic numerals (1, 2, and so on). In this article, we use the national terminologies where possible, and roman numerals are used when the country status of the Schedule is not specified. In effect, the consequences of the laws and regulations for research and treatment are roughly similar between countries. One exception is the regulations regarding cannabis, which some countries — for example, the Netherlands — have made available for medicinal use.

In the United States, a substance is classified as Schedule I if it meets three criteria[7]. First, the drug or other substance has a high potential for abuse; second, the drug or other substance has no currently accepted medical use in the United States; and third, there is a lack of accepted safety for use of the drug or other substance under medical supervision.

With regard to the first criterion, the term 'abuse' is undefined; it does not mean that the substance must possess the ability to foster dependence or addiction. This criterion could apply to any non-prescription drug that people may take if it is available. In any case, there is no evidence that psychedelics have addictive properties[8], and in fact, LSD has been used successfully to treat other addictions, as discussed below. MDMA similarly has low dependence potential[9], although some chronic cannabis users can develop dependence[10].

With regard to the second criterion, once a drug is classified under Schedule I, it is unlikely that any medical value will ever be discovered for it, because it is extremely difficult to research the drug. The argument for a drug fulfilling this second criterion thus becomes circular.

The third criterion seems to be inconsistently met, at least in the case of marijuana and psilocybin, which are listed as Schedule I. Marijuana has in fact been administered safely under medical supervision[11,12], and in the United States, medical use of marijuana is legal in 18 states and in the District of Columbia. Similarly, psilocybin has been administered to a number of subjects under medical supervision and appears to be safe for medical use (see below). These cases also show that the second criterion (that the drug or other substance has no currently accepted medical use in the United States) is inconsistently applied, as these substances are being legally used for medicinal purposes.

Importantly, there is no agreed policy for moving drugs out of Schedule I, even after medical uses have been found. That means that any research aimed at further exploring the therapeutic potential of such drugs is severely hampered.

In the United Kingdom, there is a two-dimensional approach to drug scheduling. The Misuse of Drugs Act[13] sets out controlled substances into three Classes (A, B and C). The original intention was that substances placed in Class A were the most harmful and those placed in Class C were the least harmful. This classification system was primarily used to determine the penalties for offences such as supply, production and possession of a drug. The Misuse of Drugs Regulations[14] subsequently grouped the same substances into five Schedules, which largely reflect their status in the United Nations 1961 and 1971 conventions. The UK Schedules regulate the clinical use of controlled substances as well as their storage and labelling requirements. Thus, the Misuse of Drugs Regulations determine what should be done, whereas the Misuse of Drugs Act determines what should not be done. There is little correlation between a drug's Class and Schedule[1,2].

In the United Kingdom, Schedule 1 is used for drugs that supposedly have no recognized medical use and have some (unspecified) level of harm or potential harm. As mentioned above, some of these (cannabis, psilocybin, LSD and MDMA) have been shown to have medical value (see below for more details). Indeed, cannabis was a prescription medication in the United Kingdom until the middle of the twentieth century and still is in a number of countries. As in the United States, the arguments for giving a drug Schedule I status can become self-fulfilling, as research on therapeutic uses and refutation of harms is severely impeded once it has been classified as a Schedule I drug.

The current legal status of certain substances under UK, US and international law is shown in TABLE 1.

Table 1 | **The status of certain substances in the international, UK and US legislation**

Substance	United Nations conventions	UK Misuse of Drugs Regulations	UK Misuse of Drugs Act	US Controlled Substances Act
Amphetamine	Schedule II (1971)	Schedule 2	Class B	Schedule II
Cannabis and cannabis resin	Schedules I and IV (1961)	Schedule 1	Class B	Schedule I
Cannabidiol	Not listed	Not listed	Not listed	Not listed
Cocaine	Schedule I (1961)	Schedule 2	Class A	Schedule II
2-bromo-LSD	Not listed	Schedule 1?	Class A? (uncertain)	Not listed
Heroin (also known as diamorphine)	Schedule I (1961)	Schedule 2	Class A	Schedule I
Ketamine	Not listed	Schedule 4	Class C	Schedule III
LSD (also known as lysergide)	Schedule I (1971)	Schedule 1	Class A	Schedule I
MDMA (also known as ecstasy)	Schedule I (1971)	Schedule 1	Class A	Schedule I
Methamphetamine	Schedule II (1971)	Schedule 2	Class A	Schedule II
Methoxetamine	Not listed	Schedule 1	Class B	Not listed
Psilocybin	Schedule I (1971)	Schedule 1	Class A	Schedule I
THC (also known as dronabinol)	Schedule II (1971)	Schedule 2	Class B	Schedule III
THCV	Not listed	Schedule 1	Class B	Not listed

The UK Misuse of Drugs Act (1971) categorizes drugs into three classes according to harms (A>B>C) and these determine the penalties for possession (7 >5>3 years in prison, respectively) or supply (life>14>14 years, respectively). In the United States, the situation is more complex, in that each drug has its own level of penalties applied. The United Nations conventions and the US Controlled Substances Act use roman numerals for the Schedules (that is, I, II, and so on), whereas the UK Misuse of Drugs Regulations use Arabic numerals (that is, 1, 2, and so on). LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxy-*N*-methylamphetamine; THC, Δ^9-tetrahydrocannabinol; THCV, tetrahydrocannabivarin.

Implications for neuroscience research

The widespread perception that because a substance is classified as Schedule I, it must pose a significant danger to humans still exists among law-makers and the general public — and possibly also among neuroscientists. However, this perception is generally incorrect. Importantly, the current regulations are based on this misperception and make research — both basic and clinical — hugely difficult.

For example, in the United Kingdom, it is much harder to study cannabis, MDMA and psilocybin than it is to study heroin, even though heroin is a more dangerous drug in terms of its medical and societal harms than these other drugs. However, the recognized therapeutic properties of heroin allow its medical use in the United Kingdom (although not in the United States), and hence it is placed in Schedule 2 (TABLE 1). Current UK regulations permit all hospitals to hold heroin and other opioids but require each individual hospital to obtain a licence for Schedule 1 drugs; UK Home Office data show that currently only three (out of several thousand) UK hospitals have such a licence. Applying for a licence takes about 1 year, costs many thousands of pounds and, once granted, is subject to regular police reviews. As a consequence, many researchers who would like to work on these pharmacologically fascinating substances cannot afford to do so.

Similar regulations apply in other countries. For example, it took a research group in Canada sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS) more than 4 years to obtain approvals to import MDMA from Switzerland for a trial of its therapeutic use in post-traumatic stress disorder (PTSD) in Canada, even after Health Canada (the department of the Canadian government that is responsible for national public health) and a Canadian Institutional Review Board had approved the protocol design (Canadian MDMA/PTSD Study MP-4).

The regulations apply to any quantity of a drug, so even basic researchers who use only sub-milligram quantities must comply with them. In addition, if researchers do obtain approval to use the drugs, the rules regarding the storage of the drug in the laboratory are stringent. For example, in a trial of psilocybin for patients with cancer in the United States, the researchers were required to ensure that the few milligrams of substance was weighed daily by two people to protect against theft (S. Ross, personal communication). To our knowledge, there are no examples of a significant diversion of research drugs (Schedule I or otherwise) into recreational use.

If the investigator can obtain all the necessary approvals and licences for a research study, the problem then becomes how and where to obtain the pharmaceutical substance, as these drugs are not available from standard chemical manufacturers. The cost of custom synthesis is usually prohibitively high and beyond the means of an investigator with a small grant. For example, one custom synthesis company in Boston (Massachusetts, USA) could provide psilocybin at a cost of about $12,000 per gram[15] (C. Grob, personal communication). In addition, contract synthesis companies are generally reluctant to prepare Schedule I substances because they require extensive documentation, a controlled substance manufacturer's licence and secure storage — as mandated by the DEA. This situation is particularly problematic for clinical research because: first, almost no companies have the necessary licences for the manufacture of clinically approved products (that is, products approved for human clinical administration), and second, the drug doses required in clinical research are larger than those for preclinical research, which means that the costs are significantly higher. For example, one of the authors (D.J.N.) has been quoted a minimum of £100,000 for the production of 100 doses of psilocybin for a clinical trial in patients with treatment-resistant depression.

Moreover, the 'illegal — presumed highly dangerous' perception of Schedule I drugs appears to be a powerful deterrent to grant-giving bodies. University and hospital ethics committees are similarly hesitant, and obtaining approvals for studies into these drugs is often protracted and difficult[16]. In practice, only a few funders — mostly specialized charities such as the Beckley Foundation, the Heffter Research Institute and MAPS — provide relatively small amounts of funding. This means that most of the work in this area is performed by enthusiasts who give their time for free[17]. Of the major UK and USA research funding bodies, only the UK Medical Research Council (MRC) has provided funding for a treatment trial of psilocybin in treatment-resistant depression (MRC MR/J00460x/1) through their Developmental Clinical Pathway scheme.

In practice, research with Schedule I drugs has almost completely ceased, with research into psychedelic drugs being particularly affected. The exceptions are studies that focused on identifying negative (for example, addictive or brain-impairing) properties of psychoactive drugs. In our opinion, this approach severely impairs neuroscience research and impedes the development of promising new treatments for psychiatric illnesses and other forms of mental suffering. The United Nations ban on Schedule I drug research has lasted for more than 50 years — it is difficult to think of another area of research in which regulatory constraints have had such a debilitating impact.

Unanswered scientific questions

Cannabis. Cannabis is a Schedule I drug but has been used in medicine for at least 3,000 years. Recent neuroscience research[18] has discovered that cannabinoid 1 receptors (CB1Rs) bind not only endogenous cannabinoids (endocannabinoids), such as anandamide[16], but also Δ^9-tetrahydrocannabinol (THC), the psychoactive ingredient of cannabis that makes users 'stoned'. Of particular interest for neuroscience is that CB1Rs are widely distributed in high density throughout the brain; indeed, they are the most densely expressed of the whole G protein-coupled receptor family[19].

A Pubmed search for terms related to cannabinoid receptors or endocannabinoid receptors produces many fewer hits than Pubmed searches for two other G protein-coupled receptors, namely dopamine receptors and serotonin receptors. In part, this may be due to the relative newness of these discoveries on cannabis receptors, but it may also reflect the possibility that the illegal status of cannabis and the need for licences plus safe holding inhibits research.

Despite the fact that cannabis has long been used in medicine and that its use has been recommended by eminent doctors (including the physician to Queen Victoria[20]), cannabis was put into Schedule I of the United Nations convention in 1961 on the basis of it having no medical use. This action was clearly a political rather than a scientific decision and one that has persisted since in both the United States and United Kingdom (but not in, for example, the Netherlands) despite further evidence of clinical value, as discussed below. The justification for the continued illegal status of cannabis includes claims of harms such as lung disease associated with smoking the substance, schizophrenia and addiction[21]. Such harms undoubtedly exist, but they are frequently exaggerated by scientists and the media. Overall, cannabis is less harmful than other popular drugs, such as alcohol[22].

Self-reports reveal that cannabis is commonly smoked as self-medication to improve sleep and reduce anxiety symptoms[23], and

there is growing interest in its possible use[24] in attention-deficit hyperactivity disorder. Plant-derived THC also has utility in the treatment of pain and spasticity in conditions such as multiple sclerosis and AIDS[11,12]. Other products of the cannabis plant, such as cannabidiol (CBD) and tetrahydrocannabivarin (THCV), have a pharmacology that is quite different from that of THC and may have utility in the treatment of seizure disorders, anxiety, psychosis[25] and addiction[26]. Although CBD is not a scheduled substance in the United Nations, US or UK systems, THCV is Schedule 1-controlled in the United Kingdom. The reason for this is unclear (THCV is not scheduled in the United Nations conventions); it cannot be on the basis of any pharmacological similarity to THC. Indeed, the actions of THCV may reverse the impairing effects of THC[27]. Partly because of its Schedule I status, THCV has been little studied in humans.

Medical use of marijuana has developed in the United States in the past decade and is now allowed in 17 states. It has recently been legalized for personal use in both Washington and Colorado. Nevertheless, for researchers, access to cannabis is limited, as it remains listed as a Schedule I drug. Moreover, the only source for research-grade cannabis in the United States is the National Institute on Drug Abuse (NIDA), and obtaining it for a clinical trial requires submission of US Food and Drug Administration (FDA)-approved protocols to a special 'ad hoc' Public Health Service interdisciplinary review process. Furthermore, the regulations governing the sale of marijuana to privately funded researchers explicitly state that the purpose of their research cannot be to develop the marijuana plant itself into an FDA-approved prescription medicine but must be to develop isolated cannabinoids in non-smoking delivery systems (presumably to avoid harms from smoking)[28].

In the United Kingdom, a solution of cannabis extracts containing THC and other cannabinoids, called Sativex (GW Pharmaceuticals), presented a problem for the UK authorities because THC is a Schedule 1 drug and therefore cannot be prescribed. Rather than deciding that cannabis preparations should not be in Schedule 1, Sativex was put into Schedule 4 and is now licensed for the treatment of pain and spasticity in multiple sclerosis. This decision to classify it in Schedule 4 was justified on the (pharmacologically meaningless) grounds that it was in an alcoholic solution and therefore different from other forms of THC. The decision is also inconsistent with the provisions of the 1961 United Nations convention[4]. Here, cannabis and cannabis resin are not only included in Schedule I but are also listed in the more restrictive Schedule IV of that convention[4], according to which its use does not extend to the medical treatment of people. The decision to list Sativex in Schedule 4 of the UK regulations can be seen as a pragmatic response to a messy legal situation, but it also demonstrates how current regulations impair therapeutic development. How can any producer of other cannabinoid therapeutics be sure that similar special exemptions will be made for them?

A number of synthetic cannabimimetic agents acting at the CB1R have been developed, but most will probably never be licensed as medications because they are put in Schedule I in both the United Kingdom and the United States. Moreover, despite these synthetic cannabimimetics being widely available to the general public on the black market[29], their potential addictive and therapeutic properties cannot be studied by anyone other than a Schedule I-licensed researcher. The proliferation of these new cannabimimetics with unknown toxicity was probably driven by the laws against cannabis — one of many examples of where once a drug has been made illegal, a more potent and so potentially more dangerous one takes its place. Synthetic cannabinoid agonists present two problems. First, they are often more potent than cannabis: that is, they have a higher affinity for the CB1R. Second, because of the way they are packaged (with inert vegetable material), users may inadvertently consume an overdose in a way that is much less likely to occur with cannabis or cannabis resin. It has been suggested that regulatory agencies "…curb regulation aimed at any CB receptor agonists as Schedule I, as this ignores their medicinal properties." (REF. 30) One such potential application of substituted naphthoylindoles (that is, typical cannabinoid agonists, which are currently listed as Schedule 1 in the United Kingdom) is in the treatment of glioblastomas[31].

MDMA-type stimulants. Many derivatives of amphetamine have been investigated for clinical purposes, as they have various interesting mood-altering properties. The most well-known of these derivatives is MDMA. Although first synthesized 100 years ago, it came into unofficial therapeutic use in the 1970s. Originally known as 'empathy', it was used in the United States as an adjunct to psychotherapy[32,33] owing to its ability to facilitate interpersonal communication[34]. Before the neuroscientific mechanisms of this property could be investigated, it entered youth culture in the dance/rave scene, where dealers changed the name to 'ecstasy'. The huge media backlash against this culture focused on the drug, with exaggerated claims of harm. Early stories focused on whether MDMA could produce a type of neurological damage that had been observed in rats[35], but despite years of study, there is no good evidence that occasional use has adverse neurological sequelae[36]. A number of deaths resulting from MDMA use were typically associated with hyperthermia[37], as users often danced for prolonged periods of time and failed to hydrate adequately. When the cause of these deaths became known among users, rave clubs in the United Kingdom began to offer 'chill-out' rooms and promote adequate hydration. Amazingly, in the United States, the DEA attempted to criminalize such harm reduction strategies and used them as evidence that the promoters knew that drugs were being used at their events, thus justifying DEA raids (R. Doblin, personal communication).

In the 1980s, MDMA and related compounds were Schedule I-controlled in the United Kingdom and United States and were also added to the United Nations 1971 convention on the grounds of harm. However a recent analysis showed that the publicly held view that MDMA has a relatively high fatal toxicity is incorrect[38]. MDMA use has also been claimed to lead to brain damage and memory impairment, although the evidence for these adverse effects has been questioned[36]. Indeed, a critical appraisal of the harms of ecstasy suggested that they are less than those associated with other popular recreational activities, such as horse riding[39].

Since MDMA was banned, a small group of MAPS members has campaigned to maintain interest in the potential therapeutic value of MDMA. They argue for its use as an adjunct to psychotherapy and run scientific symposia on this topic. They also completed a small scientific clinical proof-of-concept study in the United States[40], which was the first controlled clinical study of MDMA. It was conducted in patients with treatment-resistant PTSD, a severely disabling condition. They found that about 80% of MDMA-treated patients showed clinical benefits, whereas only about 20% of the placebo-treated group did. The patients were followed up for over 1 year, and the majority of MDMA-treated subjects continued to have symptomatic relief, with no subjects reporting harm from the treatment[41]. These results require replication by other research groups in other countries, which will be difficult under current regulations.

Current best practice in treatment for PTSD aims at extinction of the memories so that they no longer intrude into consciousness, but this approach requires the patient to relive the trauma and then overcome it. For many patients, the traumatic memories are so powerful and distressing that they cannot tolerate the emotions resulting from the recall, and so cannot complete the therapy. MDMA has the ability to reduce the brain responses to threats[42], which may allow patients to engage fully in the treatment. The seemingly unique ability of MDMA to enhance empathy and trust makes it a powerful (and arguably necessary) tool for studying the neuroscience of these states, but there is no other published imaging study.

There are other potential clinical uses for MDMA beyond psychotherapy for PTSD that include helping with end-of-life anxiety and couples therapy. It has been suggested that the pro-empathy actions of MDMA might help people with autism[43]. Recently, MAPS made a grant available to test this hypothesis. Other perhaps less obvious possibilities include the treatment of the disabling dyskinesias associated with L-3,4-dihydroxyphenylalanine (L-DOPA) treatment of Parkinson's disease. Animal models of Parkinson's disease suggest that 5-hydroxytryptamine (5-HT) dysregulation is involved in these dyskinesias, and the dyskinesia-reducing effect of MDMA is probably due to its enhancement of 5-HT levels[44]. Other studies suggest that MDMA facilitates the recovery of cognitive function after minimal brain trauma in mice[45]. This, to some extent, reprises results from older studies that used other stimulants in the treatment of brain injury[46] — another research area hampered by the illegal status of the possible treatments.

A more recent and equally controversial amphetamine analogue is mephedrone (also known as 4-methylmethcathinone). This drug was first synthesized in 1929, but was little used until the 2000s, when it was resurrected in Israel as an octopamine analogue to provide a biological control approach for aphids on plants (hence the slang name 'plant food'). It became widely used in Israel by young people, and although there were no reported deaths or serious harms, it was banned by the Knesset. Soon after, it spread to the United Kingdom as a 'legal high', where it went by various names such as MCAT, drone and miaow-miaow. It became very popular as it was sold in pure form (in contrast to MDMA, which was often of particularly poor quality) and, being legal, could be readily ordered over the Internet.

As with MDMA, many media articles claimed that mephedrone has dangerous adverse effects. Coupled with unfounded police suggestions that it had led to deaths, this resulted in mephedrone being banned despite the lack of any real evidence of harm[47]. It was subsequently discovered that the rise in recreational mephedrone use in the United Kingdom in fact had some unexpected benefits, particularly a spectacular fall in the number of deaths due to cocaine use by over 20% in 1 year[48]. This surprising finding could be explained by the fact that many cocaine users switched from cocaine to mephedrone, which is less toxic. Mephedrone thus seems to have saved more lives than it claimed, suggesting it has potential as a substitute for cocaine, like methadone is for heroin. Its illegal status and the fact that many analogues of mephedrone were banned under the same legislation means that this potential is now unlikely to be investigated, let alone realized.

Psychedelics. Psychedelic is a term that covers a range of drugs, but literally, it means 'mind manifesting'. Psychedelic drugs occur widely in nature: for example, in magic mushrooms (psilocybin), peyote cactus (mescaline), plant roots (ibogaine) and plant bark and certain grasses (dimethyltryptamine).

Although many scientists saw LSD as an important new tool for understanding the brain, it was never used as such because LSD was banned in the 1960s, before the emergence of modern brain science. The banning appeared to be largely driven by political concerns — namely, that American youths were using it and as a result declined to fight in Vietnam. Nevertheless, the ban was justified by claims of harms such as people dying while trying to fly or having enduring psychotic experiences[49]. Recent analyses suggest, however, that LSD is less harmful than most other controlled drugs[1,2].

LSD received much attention for its clinical uses. Between the 1950s and mid-1960s, there were more than 1,000 clinical papers discussing 40,000 patients, several dozen books and six international conferences on LSD-assisted psychotherapy[50]. Because research was stopped so early, the methods and tools were not available to examine the neurobiological basis for the efficacy of LSD. Some findings were remarkable, however. A recent meta-analysis of six studies (published before LSD was banned) into its clinical efficacy for the treatment of alcoholism found LSD-assisted psychotherapy to be at least as effective as any other available treatment[51]. In addition, LSD has been shown to help patients with a terminal illness come to terms with dying[52]. A MAPS-sponsored study of LSD in subjects with anxiety associated with end-of-life issues was recently completed in Switzerland; the results await publication.

The banning of LSD led people to search for other psychedelics that were free from the threat of legal sanctions. The most popular was psilocybin, which was (when in magic mushrooms) legal in the United Kingdom until the Drugs Act of 2005 (REF. 53). Although magic mushrooms are largely used recreationally, many individuals report using them for self-treatment of disorders such as obsessive-compulsive disorder (OCD). However, only one clinical trial has investigated psilocybin as a potential treatment for OCD[54]. That study showed marked decreases in OCD symptoms to variable degrees in all nine subjects during one or more of the testing sessions. Unfortunately, the disproportionate cost of the obtaining the drug precluded a larger follow-up study.

Another use for psychedelics is in cluster headaches, a severe pain syndrome for which treatment options are limited and which is associated with high suicide rates. Magic mushrooms and LSD are regularly used by sufferers[55], but their effectiveness in reducing pain in this condition has not been formally studied, presumably owing to their Schedule I status.

A couple of small scientific studies of psilocybin validate the view that it has therapeutic value. One study found that psilocybin administration can have profound effects on attitudes and behaviour in healthy subjects, with many subjects rating it as one of the five most significant experiences in their lives[56]. These effects were enduring; a follow-up study 2 years later revealed that the subjects still found the experience profoundly meaningful[57]. A study in cancer sufferers showed that, in a fashion similar to the value of LSD in terminal illness[52], psilocybin helped people make sense of their predicament and cope with it better[15].

Psychedelics have a particularly important role in the study of consciousness because they produce such profound changes in this state; indeed, one could argue that the psychedelic state is a major challenge for neuroscience to explain. Psychedelics act as agonists at the $5HT_{2A}$ receptor, which is most highly expressed in the cortex, particularly on layer 5 pyramidal cells, but also on fast-spiking regulatory interneurons[58]. Layer 5 neurons are thought to control top-down cortical processing of sensations[59]

and possibly emotions that are disturbed in conditions such as schizophrenia and depression. Studying the role of these receptors is impossible without using psychedelics as, to our knowledge, all 5-HT_{2A} agonists have psychedelic effects. Some 5-HT_{2A} agonists are not, as yet, controlled and therefore can be used in preclinical studies with relative ease. However, no safety data exist for these agonists, and therefore they cannot be used for studies in humans. Studies in animals have found that 5HT_{2A} agonists produce excitation of layer 5 pyramidal cells and associated interneurons[60], and in humans, 5HT_{2A} antagonists block the psychotomimetic effects of psilocybin[61]. Thus, the banning of psychedelics not only impairs research into their potential therapeutic value but also hampers basic neuroscience research.

Despite the interesting preclinical neuroscience findings listed above, very few studies using psychedelic drugs to investigate human brain function have been conducted in the 50 years since psychedelics were banned. In one recent functional MRI study, intravenous administration of psilocybin revealed a profound and unpredicted reduction in brain activity, particularly in the default-mode network, and a decoupling of the integrity of this system[62]. This effect was shown to be of neuronal origin, as it was replicated using magnetoencephalography, a technique that has sufficient temporal resolution to allow analysis of cortical neuronal circuits by dynamic causal modelling. This study showed that the main action of psilocybin was on layer 5 pyramidal neurons[63].

In some subjects in this study, psilocybin exposure was associated with enhanced mood several weeks later[64], which is consistent with findings from other studies[15,57]. Interestingly, psilocybin exposure was associated with an enhancement of visual association cortex activation in response to positive memories, which might help to explain the positive mood outcomes[64]. The psychosis-like state induced by psilocybin could also be used to test new antipsychotics, as the default-mode uncoupling it produces is similar to that observed in individuals with prodromal schizophrenia[65].

These findings have implications for the treatment of mood disorders, and the UK MRC has funded a trial of psilocybin-augmented psychotherapy for treatment-resistant depression. However, the trial has been unable to begin because no supplier of trial quality (good manufacturing practice (GMP)) psilocybin has been found. (Current UK Medicine regulations require GMP production of substances for clinical trials but allow neuroscience experiments to be performed with chemically pure non-GMP products.) Even if the trial does start and has a positive outcome, roll-out of psilocybin into wider clinical research and treatment will be almost impossible in either the United Kingdom or United States without a change in the law, because any doctor wishing to prescribe the drug treatment would need to obtain a Schedule I licence — at great cost and time, as explained above.

TABLE 2 summarizes the actual and potential uses and neuroscience interests for many of the substances discussed here.

The role of neuroscientists

From the above, it is self-evident that the laws relating to Schedule I drugs have had a deleterious impact on the progress of neuroscience research and treatment development. The therapeutic potential of these drugs is clear, but further investigation is hampered by the hurdles and costs that these regulations impose. Perhaps more important for the neuroscience community is the fact that human brain studies on phenomena such as hallucinations and consciousness and the role of the 5HT_{2A} receptor have been impeded by these regulations.

There is a third facet to the drug regulations: namely, that research into potential harms of the drugs is hampered. In all Western countries, the legal justification for the regulation of drugs is to reduce harms. It is more difficult to estimate the extent of harms of illegal drugs than those of legal drugs because data collection for illegal drugs is much poorer. Moreover, research into the possible harmful effects of these drugs, with the aim to improve treatment and to prevent these harms, is also impaired by current regulations. Research on opioids, such as heroin, and stimulants, such as cocaine, has substantially improved our understanding of the brain mechanisms of addiction[66] and has led to new treatments, such as buprenorphine (Subutex, Reckitt Benckiser) for heroin addiction[67]. That has not happened for the drugs discussed in this article, partly because of their Schedule I status. If we understood the effects of these drugs better, then we might be able to develop analogues that maintain therapeutic potential but have fewer adverse effects. In the United Kingdom, heroin is classed in Schedule 2 and is therefore easier to study than cannabis or psilocybin. In the United States, it is classed as Schedule I and so is hardly studied there at

Table 2 | **Schedule I drugs — potential uses and neuroscience interests**

Drug	Therapeutic uses	Potential therapeutic uses	Neuroscience research interests
Cannabinoid THC	• Spasticity • Pain • Appetite stimulation	• Attention-deficit hyperactivity disorder • Post-traumatic stress disorder • Insomnia	• Nature of consciousness • Model of psychosis • Mechanisms of pain and appetite
Cannabinoid THCV		• Anxiety • Insomnia	• Emotion regulation
Ketamine	• Anaesthesia • Analgesia • Depression		• Glutamate (NMDA) receptor function • Model of psychosis
LSD	• Cluster headaches • Terminal illness	• Pain syndromes • Alcoholism	• Model of psychosis • Nature of consciousness • Perceptual processes • 5-HT receptor function
MDMA	• Psychotherapy for post-traumatic stress disorder	• Couples psychotherapy • Parkinson's disease • Brain recovery	• Emotion regulation • Empathy • 5-HT_2 receptor function
Mephedrone		• Cocaine dependence • Other stimulant addiction	• Stimulant function • Addiction
Psilocybin	• Obsessive-compulsive disorder • Cluster headaches • Terminal illness	• Depression	• Nature of consciousness • Perceptual processes • Model of psychosis and mood • 5-HT_2 receptor function

5-HT, 5-hydroxytryptamine; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxy-*N*-methylamphetamine; THC, Δ^9-tetrahydrocannabinol; THCV, tetrahydrocannabivarin.

all. Cocaine is not in Schedule I in the United States because it has a medical use as a local anaesthetic in, for example, ocular surgery.

Governments maintain that current drug regulations do not prevent research because people have the opportunity to obtain licences. In practice, however, there has been a *de facto* ban on research into many psychoactive drugs over the past 50 years for the reasons described above. In the case of psychedelics, there has been almost no research since the ban, in marked contrast to the situation before it. This ban derives from the enforcement agencies assuming authority over the scientific community, as exemplified by the questions posed by Robert F. Kennedy to the DEA in the 1960s (quoted in REF. 49):

> *Why if [clinical LSD projects] were worthwhile six months ago, why aren't they worthwhile now? … We keep going around and around … If I could get a flat answer about that I would be happy. Is there a misunderstanding about my question?* Robert F. Kennedy

One can only hope that the inhibition of research has not been viewed by governments as a convenient protection against evidence-based challenges to the current scheduling. The lack of new evidence perpetuates the justification for severe controls on these drugs on the basis of the precautionary principle. One of us (D.J.N.) has met seeming resistance to our work on psilocybin and MDMA from a UK politician who has tabled parliamentary questions that challenge the value of our research and ask how it could be terminated[68]. It seems that it is difficult for some politicians to understand that a psychoactive drug (like any substance) can have both beneficial and adverse effects, and that perspective has resulted in the current cautious policy in terms of the regulation of such drugs.

It is surprising that the scientific community, particularly neuroscientists, has not protested against the effective ban of research on drugs that could offer so many insights into human brain function and such great opportunities for new treatments. Most of the funded and published research into these drugs seems to focus on their possible harms rather than their possible benefits. This focus may reflect a genuine concern that researchers have in relation to public health, but it can bias legal opinion. Remarkably, the only paper on MDMA in a leading scientific journal in the past 20 years was one purporting to show that it caused dopaminergic brain damage, and this finding was later retracted after it emerged that the investigators had used methamphetamine by mistake[35]. The fact that the peer reviewers of the paper apparently did not notice that the result was pharmacologically implausible could suggest that there may be presumptive prejudice about these psychoactive drugs even among some scientists.

Importantly, this now retracted study was used, along with other studies, to justify the decision by the US Sentencing Commission to increase the penalties for MDMA possession 14-fold (to 2.5 times those of cocaine possession). This decision was based on MDMA's purported neurotoxicity, addictive propensity and its being doubly harmful, as it could be classed both as a hallucinogen and a stimulant. A recent court case in New York has resulted in a major revision of this policy, with penalties now being equal to those for cocaine possession, following evidence that MDMA was not neurotoxic, not addictive and not a hallucinogen[26]. Judge Pauley, when making this judgement, attacked the US Sentencing Commission's decision, criticizing them for "opportunistic rummaging" of supposed scientific facts and noting their "selective and incomplete" analysis, particularly considering that MDMA is one of the least addictive of drugs[69].

There are other examples of therapeutically promising drugs that are difficult to research owing to regulations. A pertinent recent example in the United Kingdom is ketamine analogues such as methoxetamine (BOX 1).

Conclusions and future directions

If some of the substances described above are to achieve their status as potential therapeutic agents, they would have to be moved to a lower — that is, less restrictive — Schedule in the drugs legislation. In the United States, simply moving these substances from Schedule I to Schedule II would make them much more accessible for research. For MDMA and psilocybin, however, that would be difficult because both are also placed in Schedule I of the United Nations 1971 convention. Thus, changing their status requires approval by a majority of United Nations Member States, and the United Nations conventions have proved to be extremely resistant to any such changes. The (neuro) scientific community can help to change the situation by making the case for such changes to their governments.

In the meantime, individual countries could exempt hospitals and other research organizations from the need to apply for Schedule I licences, as is currently the case in the United Kingdom for Schedule 2 drugs such as heroin. Also, at least in the United Kingdom, many substances in Schedule 1 of the Misuse of Drugs Regulations are not under international (United Nations) control. These include, for example, certain substituted derivatives of cathinone[70] and ketamine as well as certain (legally ill-defined) derivatives of LSD, such as 2-bromo-LSD (which does not have psychedelic properties but appears to be effective in treating cluster headaches)[71]. In principle, these could all be moved to a

Box 1 | Ketamine and methoxetamine

Ketamine is a glutamate NMDA receptor antagonist that has been used for decades as a tool in neuroscience research on glutamate systems. Clinically, it is a unique, respiration-sparing anaesthetic that is particularly useful for children, on the battlefield and in veterinary practice. It also has a growing role in the treatment of chronic pain syndromes[72] and has been acclaimed as the most important advance in the treatment of depression for the past 50 years[73]. However, for some time there has been growing recreational use of ketamine, which has led to some deaths and an emerging problem of chronic inflammatory cystitis that can lead to the need to remove the bladder[74]. For these reasons, safer alternatives to ketamine would be preferred and one — methoxetamine — has been developed and sold over the Internet. It is a dissociative anaesthetic showing rapid-acting antidepressant effects and is thought to be both a non-competitive NMDA receptor antagonist and a dopamine reuptake inhibitor[75]. Although no deaths have been associated with methoxetamine use so far, the UK government's Advisory Council on the Misuse of Drugs recommended banning it in 2013 (REF. 76). To prevent other analogues being substituted for methoxetamine, they also recommended making a whole range of similar compounds illegal, most of which have never been tested in rodents, let alone used in humans. Although ketamine is listed in Schedule 4 in the United Kingdom, these analogues were put into Schedule 1, which will inevitably severely limit studies to determine whether they might in fact be safer alternatives to ketamine. Even more confusing was the decision to put the analogues in Class B of the UK Misuse of Drugs Act, so attracting penalties of up to 5 years in prison for possession and 14 years for supply, whereas for ketamine the penalties are 2 and 7 years, respectively[76]. This categorization is scientifically flawed; if the alternatives are safer than ketamine but never become available, this ban may also paradoxically increase the use and harms associated with ketamine use.

lower Schedule by domestic action without reference to the international drug control treaties.

As discussed above, preclinical research could be performed more easily if a licensing category was created in the law especially for scientists who need only small amounts of drug. *In vitro* studies and studies in animals require only a few milligrams of most substances, and even less with LSD. If the quantity on hand for research is less than a single human dose, one could argue that diversion control is not necessary in these cases.

The contrast with the situation for drugs such as heroin and methamphetamine is profound. A lot of research is done with these, mainly in animals, with the aim of understanding the brain changes that underlie addiction and relapse. If these substances are allowed in the laboratory both because they are addictive and despite them being addictive, would it not make sense to encourage research on other psychotropic drugs that have less strong (or even no) addictive properties?

We finish with an insight from one of the pioneers of using drugs to explore the nature of consciousness — Aldous Huxley — whose words about the suppression of justice have considerable resonance with the restraint of neuroscience research discussed in our paper.

Great is truth, but still greater, from a practical point of view, is silence about truth. Facts do not cease to exist because they are ignored. By simply not mentioning certain subjects … totalitarian propagandists have influenced opinion much more effectively than they could have by the most eloquent denunciations. Aldous Huxley

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